

Amendments to the Specification:

Please delete the paragraph beginning on line 25 of page 8 and ending on line 27 of page 8 and replace it with the following new paragraph:

Figure 1 depicts the structure of the tricyclic cytosine analog G-clamp, its extended analog guanidino G-clamp hybridized to complementary guanosine, and a palindromic decamer duplex that was used for x-ray crystallography (SEQ ID NO:57).

Please delete the paragraph beginning on line 1 of page 126 and ending on line 12 of page 126 and replace it with the following new paragraph:

Phenoxazine **151** and G-clamp **152** nucleosides were prepared by modifying previously published procedures [Lin, K.-Y.; Jones, R. J.; Matteucci, M. *J. Am. Chem. Soc.* **1995**, *117*, 3873-3874; Lin, K.-Y.; Matteucci, M. *J. Am. Chem. Soc.* **1998**, *120*, 8531-8532]. The succinates **153** and **154** and the corresponding substituted solid supports **155** and **156** were prepared as outlined in Scheme 19. Using the CPG supports, the two cytidine analogs **151** and **152** were incorporated at the 3'-terminus of two model oligonucleotides **157** and **158**, respectively, with the sequence T₁₈dC* (dC* = phenoxazine (~~SEQ ID NO:62~~ SEQ ID NO:54) or G-clamp deoxyribonucleoside (~~SEQ ID NO:63~~ SEQ ID NO:55)). Solid phase oligonucleotide syntheses was carried out using standard phosphoramidite chemistry. Deprotection of G-clamp containing oligonucleotide **158** was performed with a 1:1 solution of MeNH₂ (40%, aq.) and NH₃ (28-30%, aq.) at r.t. for 4 h. The oligonucleotides were purified and desalted by reversed phase HPLC.

Please delete the paragraph beginning on line 13 of page 126 and ending on line 24 of page 126 and replace it with the following new paragraph:

Snake venom phosphodiesterase (SVPD) and bovine intestinal mucosal phosphodiesterase (BIPD), were utilized as the hydrolytic enzymes for *in vitro* nuclease resistance studies. Both enzymes predominantly exhibit 3' exonuclease activity. An unmodified 19mer oligothymidylate (oligonucleotide **159**) (~~SEQ ID NO:64~~ SEQ ID NO:56) was used as a control. Oligonucleotide samples were incubated with SVPD (2.5 units/μmol substrate) or BIPD (0.55 units/μmol substrate) in 50 mM Tris-HCl, 8 mM MgCl₂ buffer, pH

7.5 at 37°C. At certain time points aliquots of 10 µl were removed and heated in boiling water for 2 min to inactivate the enzyme. Subsequently, the samples were desalted by membrane dialysis against Nanopure deionized water using Millipore 0.025 µm VS membranes and stored frozen until they were analysed. The progress of enzymatic degradation was monitored by capillary gel electrophoresis (CGE).

Please delete the paragraph beginning on line 3 of page 128 and ending on line 14 of page 128 and replace it with the following new paragraph:

Phenoxazine **151** and G-clamp **152** nucleosides were prepared by modifying previously published procedures [Lin, K.-Y.; Jones, R. J.; Matteucci, M. *J. Am. Chem. Soc.* **1995**, *117*, 3873-3874; Lin, K.-Y.; Matteucci, M. *J. Am. Chem. Soc.* **1998**, *120*, 8531-8532]. The succinates **153** and **154** and the corresponding substituted solid supports **155** and **156** were prepared as outlined in Scheme 19. Using the CPG supports, the two cytidine analogs **151** and **152** were incorporated at the 3' terminus of two model oligonucleotides **157** and **158**, respectively, with the sequence T₁₈dC* (dC* = phenoxazine (~~SEQ ID NO:62~~ SEQ ID NO:54) or G-clamp deoxyribonucleoside (~~SEQ ID NO:63~~ SEQ ID NO:55)). Solid phase oligonucleotide syntheses was carried out using standard phosphoramidite chemistry. Deprotection of G-clamp containing oligonucleotide **158** was performed with a 1:1 solution of MeNH₂ (40%, aq.) and NH₃ (28-30%, aq.) at r.t. for 4 h. The oligonucleotides were purified and desalted by reversed phase HPLC.

Please delete the paragraph beginning on line 15 of page 128 and ending on line 26 of page 128 and replace it with the following new paragraph:

Snake venom phosphodiesterase (SVPD) and bovine intestinal mucosal phosphodiesterase (BIPD), were utilized as the hydrolytic enzymes for *in vitro* nuclease resistance studies. Both enzymes predominantly exhibit 3' exonuclease activity. An unmodified 19mer oligothymidylate (oligonucleotide **159**) (~~SEQ ID NO:64~~ SEQ ID NO:56) was used as a control. Oligonucleotide samples were incubated with SVPD (2.5 units/µmol substrate) or BIPD (0.55 units/µmol substrate) in 50 mM Tris-HCl, 8 mM MgCl₂ buffer, pH 7.5 at 37°C. At certain time points aliquots of 10 µl were removed and heated in boiling water for 2 min to inactivate the enzyme. Subsequently, the samples were desalted by

DOCKET NO.: ISIS-4804

PATENT

Application No.: 09/996,292

Office Action Dated: September 27, 2004

membrane dialysis against Nanopure deionized water using Millipore 0.025 μm VS membranes and stored frozen until they were analysed. The progress of enzymatic degradation was monitored by capillary gel electrophoresis (CGE).

Please delete the sequence listing filed March 29, 2002 and replace it with the amended sequence listing being filed concurrently herewith.